RENAL LESION AFTER SINGLE INJECTION OF CADMIUM IN RABBIT

A group of rabbits received a single injection of cadmium chloride, and development of renal and hepatic lesions were followed up for two years. Renal lesion became apparent after one year under routine light microscope.

Rabbits were of male Japanese White weighing 2~3 kg at the time of injection. They were housed in steel wire mesh cages individually, and were fed with commercial pellet CF-1 and tap water ad lib. A single injection of cadmium chloride of 3 mg/kg as cadmium was administered subcutaneously at the interscapular resion. After an injection, the animals were sacrificed at variable intervals up to two years.

Cadmium contents in the kidney and liver were determined by atomic absorption spectrometer. Those results were plotted in the Fig. 1. Evaluation of the lesion was done on routine paraffin embedded, H.E. stained sections. Criteria used for grading of renal lesions of the "chronic type" have been described in foregoing paper.¹⁾

Fig. 1. Cadmium contents in kidney and liver of rabbit after single injection.

In the kidney, gradual development of generalized cloudy swelling of the proximal convolution was a main feature during the first week after the injection. Bizarreness of the apical cytoplasm was also noticed. However, there was neither necrosis nor hydropic degeneration, which are typical feature of renal lesion of "acute type." Those so-called "non-specific" changes gradually subsided thereafter, and the kidneys from five months after injection showed entirely normal appearance.

When the kidney was examined after one year, pathy areas of tubular atrophy in the deep cortex were noticed in two out of three animals. In this foci, proximal con-

voluted tubules were slightly dilated and their epithelium were flat and atrophic. Surrounding interstitium was slightly distended and edematous. Those features are quite identical with those of early stage of chronic type renal lesion corresponding to grade 1 after the author's criteria.

After more than one year, succeeding development of renal lesion was rather variable by case. One animal sacrificed at 16 months showed a little advanced lesion of grade 2 (Fig. 2). Another 17 months animal of grade 1 was complicated by slight to moderate amyloidosis. In an animal of 19 months, there was extensive amyloidosis with marked glomerular involvement (Fig. 3). One from 21 months was grade 1~2. On the other hand, however, lesion of an animal of 24 months remained still at a stage of grade 1.

Although the number of animals is small, the above findings suggest that a single dosage of cadmium may develop renal lesions during succeeding course of life of animals. It was noteworthy that the lesions become apparent when rather a long time elapsed after the administration of the cadmium. Changes in the liver were not remarkable under routine light microscope, except for typical amyloid lesion in two animals.

In accord with the analysis of metal content,²⁾ the liver cadmium increased at the early stage and reached the maximum concentration within two weeks. Thereafter, the concentration decreased slowly. In contrast, the kidney cadmium showed a steady increase up to one year. Then the concentration retained almost the same level during the further observation time. This gradual rise in the kidney cadmium seems to be roughly corresponded to the decrease in the liver. It may be probable that the renal cadmium was mainly supplied from the cadmium stored in the liver.

When the earliest renal lesion was noticed, corresponding renal cadmium was around 100 ppm. A case of severe amyloidosis showed extraordinarily low cadmium concentration.

Late occurrence of chronic type renal lesion after secession of cadmium exposure has been referred in foregoing reports,¹⁾ which were done under daily administration in using sufficient amounts to produce typical acute renal lesions, i.e. hydropic swelling and acidophilic necrosis of the proximal convolution at the end stage of the administration schedule. Because of severity of their renal lesions, suspicion was remained whether late development of chronic type renal lesion might be somehow caused by the foregoing acute type lesions. The present observation has no such possibility, because in this experimental condition, dosage was low and simplified as not to develop the acute changes.

Those past and present results show, if sufficient amounts of cadmium were once stored, mainly in the liver, any renal lesion may be developed later without succeeding additional exogenous burden. It is important that the late renal lesion of "chronic" type could be induced by the stored cadmium alone.

When cadmium workers were removed from exposure or their working environment were improved, improvement of urinary findings was noticed as described by Tsuchiya³⁾ as well as by Harada.⁴⁾ On the other hand, some earlier reports⁵⁾ cited literature reporting late occurrence of proteinuria in the workers who had been removed from the exposure for several years. Discrepancies among those results may be explained by the

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Fig. 2. Slight atrophy of the proximal convoluted tubule in a rabbit sacrificed at 16 months after single injection.

Fig. 3. Proximal convolution around two glomeruli are slightly dilated and the epithelium are atrophic. Nineteen months after single injection. Slight amyloidosis was complicated.

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late onset of renal lesions as observed in the present observation.

As described in another paper,²⁾ the most part of cadmium in the kidneys as well as in the liver at every stage was found in the metallothionein fractions. Thus to explain the mechanisms of late onset of renal lesion of chronic type, metallothionein may reasonably be the first candidate to exert its injurious effect to the kidney. Data available on the toxicity of metallothionein bound cadmium has been still a few and the results were somewhat controversial. Originally, metallothionein production and its sequestering capacity of cadmium has been accepted as a reasonable explanation for the development of tolerance phenomenon in an acute intoxication. This consideration is based on the assumption that cadmium may be inactivated when it was bound to metallothionein. In fact, in vitro experiment, toxicity of the cadmium-metallothionein to the isolated renal mitochondria was proved to be negative, in sharp contrast to marked toxic activity by ionic cadmium itself.⁶⁾ Recently, Nordberg *et al.*⁷⁾ demonstrated in vivo toxicity of metallothionein bound cadmium when it was injected subcutaneously or intravenously to mice in a rather large amount.

It may be interesting to see what kind of renal lesion could be produced in long lasting administration of metallothionein cadmium in more lower doses. In this regard, it seems also important to elucidate more detailed in vivo metabolism and fate of metallothionein, especially to know what happens during translocation from the liver to the kidney. Recent data obtained by Suzuki⁸⁾ who found different composition of metallic elements in the metallothionein fraction between visceral i.e. the liver and kidney, and blood, suggest the above possibility. At the same time, any possible roles of cadmium in the "non-metallothionein" form should be considered, as another important aspect of this problem, in view of their renal toxicity and carrier in transportation.

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